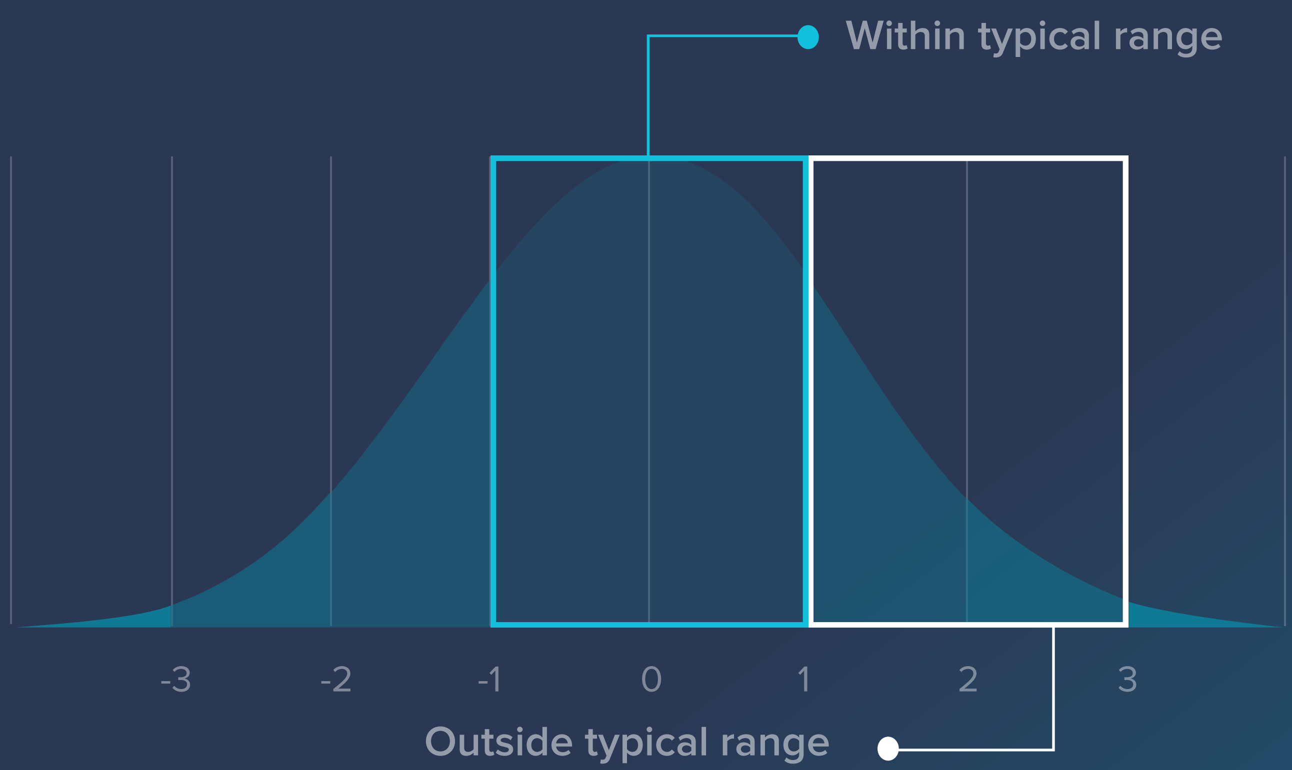


CREYOS ADHD CLINICAL PROTOCOL AND REPORT

Science Guide

Quickly gain validated and powerful brain health insights

Important Information Before You Read This Document

Creyos (formerly Cambridge Brain Sciences) provides a scientifically-validated and objective measure of an individual's cognition, however, it is not a diagnostic tool. Creyos Health should be used in conjunction with other information and clinical judgment to reach conclusions regarding an individual's health. Ultimately, Creyos Health does not replace the judgment of a practitioner and Creyos does not assume responsibility for the outcome of decisions made based on Creyos Health data.

The Science Behind the Creyos ADHD Assessment

This guide is meant to explain the scientific underpinnings of the Creyos ADHD protocol and report. Within this guide you'll get a breakdown of how the protocol was developed, including the background research conducted, elements included within the protocol, and the markers associated with ADHD. This guide is meant to serve as a resource to help you better understand how the protocol works so you can feel confident in its ability to help you assess patients for ADHD.

A. Cognitive Testing and ADHD

Attention deficit hyperactivity disorder (ADHD) is common in children and adults, but can be difficult to diagnose. Clinicians require as much information as possible to come to a final decision about the presence and severity of symptoms in a specific patient. Deficits in attention and executive function are key signs of ADHD, but objective information about them is often lacking, forcing clinicians to move forward without complete evidence-based justification for diagnosis and treatment. Neuropsychological testing can provide information that potentially improves clinical outcomes and quality of life for patients with concerns about attentional difficulties (Pritchard et al., 2011).

The Creyos ADHD protocol quickly assesses cognitive function through a series of scientifically validated performance indicators called markers, each linked with attention deficit hyperactivity disorder. This guide explains the science behind the protocol, including how markers were chosen, validity of the approach, and studies linking each marker to ADHD.

For an overview of the elements of the ADHD protocol and interpretation tips, see the Creyos ADHD Clinical Report Interpretation Guide.

B. Finding Cognitive Task Markers Associated With ADHD

The Creyos ADHD protocol is focused on markers—specific cognitive performance metrics within Creyos tasks that are associated with an ADHD diagnosis. To find markers validated through scientifically-supported associations with ADHD, Creyos examined over 100 peer-reviewed papers involving its core battery of 12 cognitive tasks. An additional task, the SART, is also included in the ADHD protocol to measure aspects of sustained attention.

Research supported 14 markers clearly associated with ADHD, each derived from one of the core 12 Creyos cognitive tasks or the SART. Each marker was used in several studies demonstrating a statistically significant difference between individuals diagnosed with ADHD by a healthcare professional and individuals from a typically developing or healthy control population. In other words, people diagnosed with ADHD perform differently on each marker.

Sample research sources for each marker are available directly in the Details Section of each report, and additional details are outlined below in Section D.

Marker Performance and Thresholds

Performance on each marker is presented on the report in raw units, such as milliseconds or the number of errors. For example, a report may display “5 errors on Feature Match.” But how can clinicians know if 5 errors is high or low for the patient’s age and gender? That’s where thresholds come in.

Each marker has a threshold based on the Creyos normative database. **The threshold represents one standard deviation away from the mean, in the direction of individuals diagnosed with ADHD.**

Cognitive Assessment Details

Planning

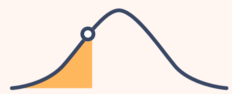
Spatial Planning

A measure of planning — the ability to act with forethought and prepare a sequence of steps to reach a goal. Common everyday activities associated with planning include:

- Deciding the order of items to pack in a trunk or moving van.
- Organizing your schedule to effectively balance work, chores, and social life.
- Planning where to put your hands and feet when rock climbing.
- Building or assembling furniture without any instructions.

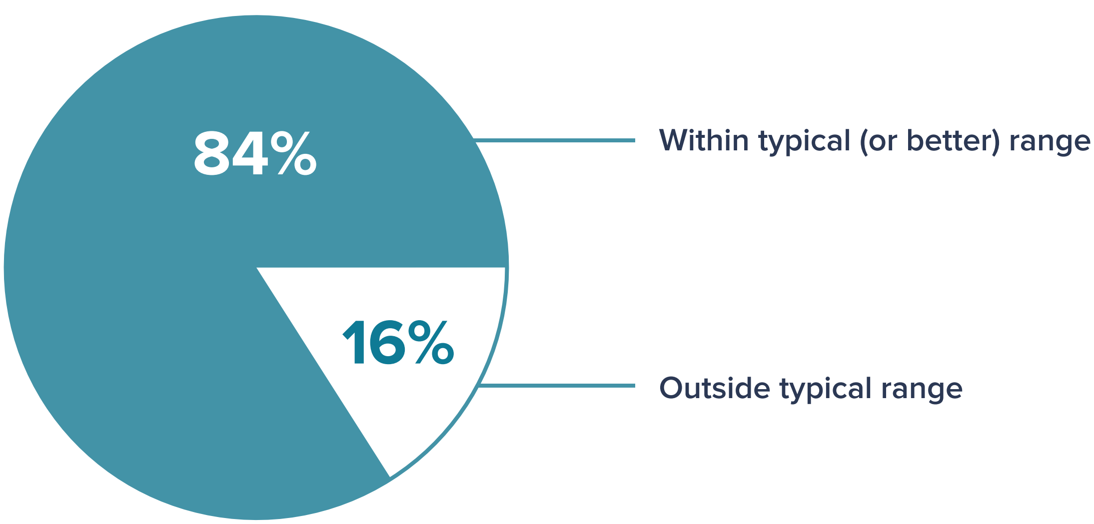
Overall Score

Overall planning ability, indicating the ability to arrive at a planned solution quickly and accurately. Some people with ADHD perform poorly on planning tasks, but deficits may be context-dependent and inconsistent.



Result	1
Typical Range	> 12
Percentile	15

One standard deviation (SD) is, roughly, the typical distance from the mean, so **individuals who are more than one standard deviation away from average can be considered to have scored atypically**. This threshold is common in research and clinical practice. For example, Golden et al. (2000) suggest that when interpreting objective task performance, further investigation is appropriate when results are more than 1 SD away from the mean. Approximately 84% of individuals in the population fall within the typical (or better) range, and 16% fall outside the typical range. Identifying and counting atypical aspects of cognition may help objectively confirm cognitive symptoms reported by a patient.



C. Validity and Reliability of the Protocol

Validity and Reliability of Core Creyos Tasks

The 12 core Creyos tasks have been validated over the course of decades of research. Validity has been established in **over 300 studies, including patient studies, brain imaging research, and large-scale online projects involving tens of thousands of participants**.

More information about each task's validity and reliability can be found in the Creyos Health Science Overview. Further validation through brain imaging can be found in the Creyos Brain Regions Guide.

Is online ADHD testing valid?

Computerized testing has become widespread, but there may be concerns that testing completed over the Internet and/or without supervision results in less valid or reliable data compared to in-person testing.

Care should be taken to ensure every patient devotes effort to the testing session, whether it is completed in-person or online. Creyos includes written instructions to reduce noise and distraction, and some clinicians provide their own guidance when introducing cognitive assessments. If there are concerns that an individual patient cannot complete testing without supervision, all Creyos assessments can be completed in person. In the context of ADHD testing, some distraction may be expected whether the assessment is completed at home or in clinic, and result in the assessment being able to capture lapses due to the patient's condition.

Creyos has not detected systematic differences between in-person and online testing in patient populations or healthy controls (Sternin et al., 2019). Regarding the SART specifically, continuous performance tasks have similar validity and reliability across settings (Raz et al., 2014), but errors and slower reaction times may be slightly more common in a home setting.

Validity and Reliability of the SART

The SART has proven to be a valid and reliable measure of sustained attention. In the context of ADHD, validation is primarily established by strong links between various SART-based markers and professionally diagnosed ADHD (see Section D). Aside from that primary validation, the SART is sensitive to known brain damage (Manly et al., 2003), and used to study the role of areas such as the anterior cingulate cortex, dorsomedial prefrontal cortex, and ventromedial prefrontal cortex in sustained attention (Christoff et al., 2009).

The SART requires patients to pay close attention and respond after every number that appears —except the number 3.

In a meta-analysis and study performed by Smilek, Carriere, and Cheyne (2010), real-world implications of the SART were established by a significant correlation between SART commission errors and the Cognitive Failures Questionnaire, a self-report questionnaire capturing everyday failures and slips in cognition. Other real-world measures of attention errors also correlated with various SART markers.

Regarding convergent validity, the SART is similar to, and correlated with, other well-known continuous performance tasks (CPTs) used to measure sustained attention and assist with ADHD assessment. For example, in one study (Raz et al., 2014) all markers from a high-target CPT similar to the SART correlated significantly with corresponding markers on the Conners Continuous Performance Test. The SART is also similar to the Test of Variables of Attention (TOVA), and particularly the second half that contains more targets than nontargets. Despite small differences in stimuli, timing, and duration, most CPTs measure similar attentional abilities, and the SART strikes a balance between collecting valid data and taking as little time as possible.

The SART's reliability has also been established—the original authors found good test-retest stability over a period of 1 to 2 weeks (Robertson et al., 1997), and Raz et al. (2014) found that a continuous performance task similar to the SART had split-half reliabilities of 0.83 to 0.98 both at home and in a laboratory.

Psychometric properties are steady across multiple patient populations, countries, and languages. Unlike many other cognitive tasks, even age, gender, and education appear to have minimal impact on SART performance (Chan, 2009).

Device Requirements for the SART

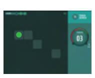
Testing done with patients' own personal devices is generally accurate. Browsers are able to display and record the simple information involved in the SART almost instantly, so computer specs do not affect accuracy. The user's own CPU provides timing information, so the integrity of data does not depend on Internet speeds.

Using a wireless input device can introduce some amount of variation in reaction times. **Patients and clinicians are encouraged to use wired or built-in devices** (e.g., a mouse or keyboard connected with a USB cable, or a laptop trackpad) if possible when the ADHD protocol is administered.

The Creyos Normative Database

Thresholds for the typical range of each marker are calculated based on the Creyos normative database. The main database contains over 85,000 individuals. Additional data from 6,395 individuals participating in various scientific studies formed the basis of norms for the SART task. Due to its size and careful methodology to collect representative data, the Creyos database confidently represents a generally healthy normal population. Marker thresholds for core cognitive tasks are based on the mean and standard deviation within the patient's age group in the normative database. Note that SART norms are not currently broken down by age group or gender—the effects of age and gender on SART performance are minimal in both healthy and patient groups (Chan, 2009). For additional details, see Understanding the Creyos Health Normative Database.

Cognitive Assessment Details



Spatial Working Memory

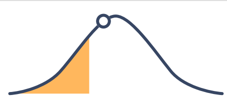
Token Search

Measures working memory — the ability to temporarily hold information in mind and manipulate or update it based on changing circumstances or demands. Common everyday activities associated with spatial working memory include:

- Systematically searching for a lost item in your home.
- Solving a mystery by remembering a set of clues, then rearranging them in your mind to tell a story and form a theory.
- Finding the most efficient way to complete a to-do list of tasks around your home before leaving in the morning.
- Efficiently navigating shifting priorities at work.

Average Score

The average number of items that could be stored and manipulated in memory. Spatial working memory is a key component of executive function. People with ADHD tend to be impaired on complex spatial memory tasks, indicating executive dysfunction in addition to attention-specific deficits.



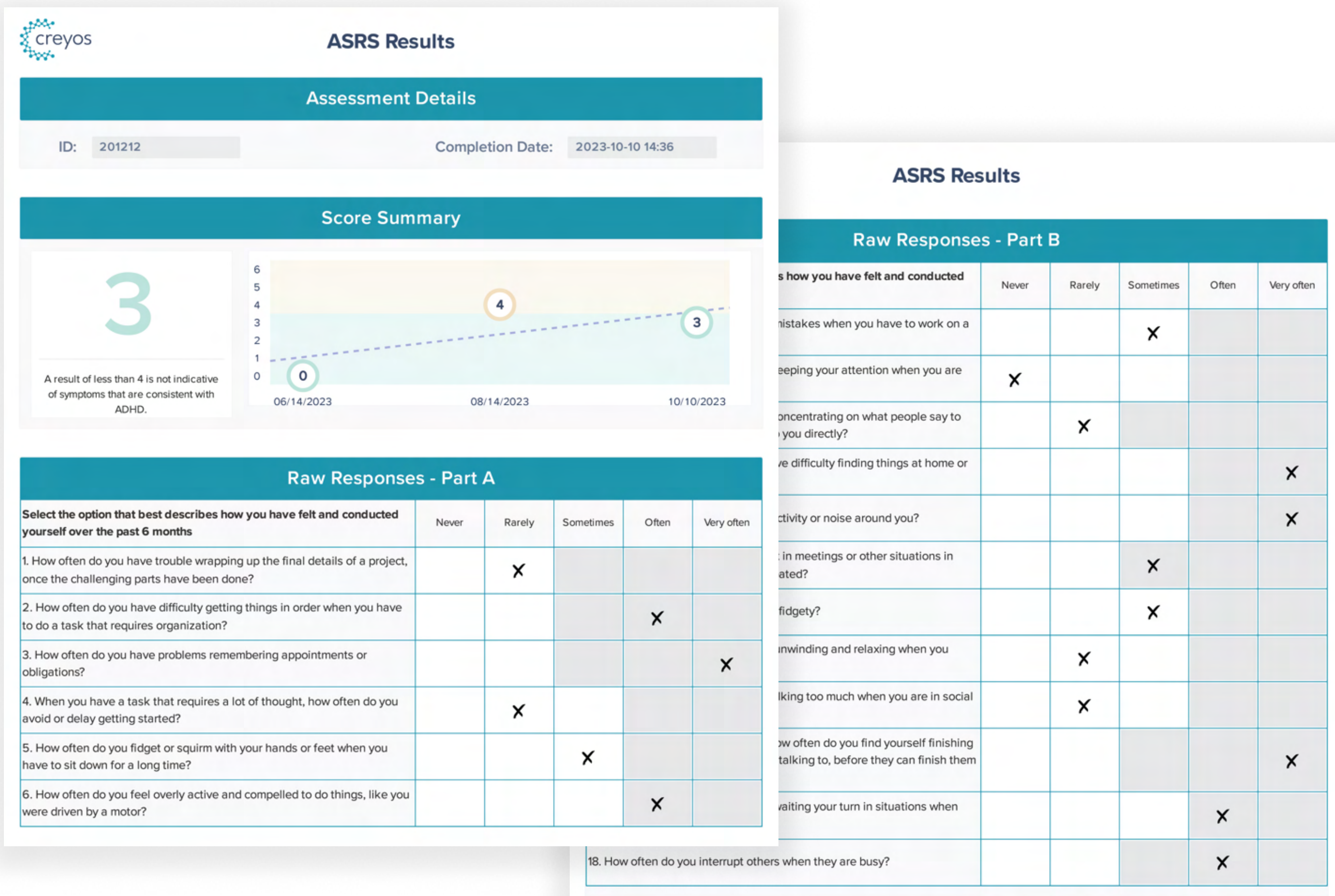
Result	4
Typical Range	> 4.83
Percentile	23

Alderson, R. M., Kasper, L. J., Hudec, K. L., & Patros, C. H. G. (2013). Attention-deficit/hyperactivity disorder (ADHD) and working memory in adults: A meta-analytic review. *Neuropsychology, 27,* 287–302.

ADHD Questionnaires

The ADHD protocol includes one of three ADHD questionnaires, automatically chosen based on the patient's age:

- Age 6 to 11: The Vanderbilt ADHD Diagnostic Rating Scale (VADRS)
- Age 12 to 17: The Strengths and Weaknesses of Attention-Deficit/Hyperactivity-symptoms and Normal-behaviors (SWAN)
- Age 18+: The Adult ADHD Self-Report Scale (ASRS)



Each questionnaire is a standard third-party questionnaire commonly used to assess subjective attention-related symptoms. For more information on the origins of each questionnaire, psychometric properties, validation, and other information, see each of the articles linked above.

Sensitivity and Specificity of the ADHD Protocol

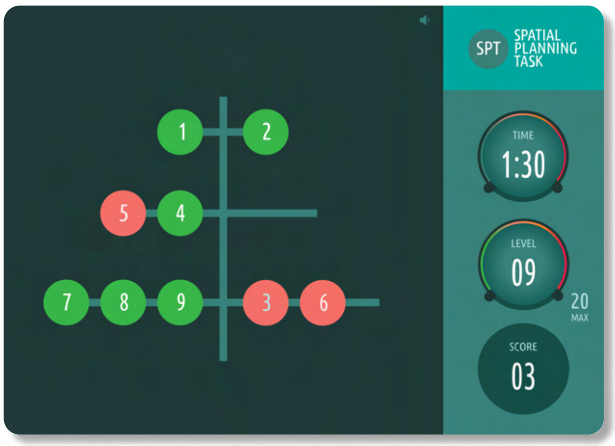
Sensitivity and specificity are values describing the accuracy of a test for the presence or absence of a condition. However, the Creyos ADHD protocol is not a standalone diagnostic tool, and does not provide cutoffs for the presence or absence of ADHD. Therefore, sensitivity and specificity cannot be calculated for this protocol. Ultimately, diagnosis is a clinical decision based on multiple sources of information, including cognitive tasks and questionnaires, but also direct patient observation, interviews, and clinical training. Clinicians typically use Creyos Health as one part of a comprehensive process designed to maximize accurate detection of ADHD.

Generally, the addition of cognitive testing to simple behavioral checklists improves detection of ADHD. For example, Holmes et al. (2010) found that response inhibition and memory tasks provided high levels of discrimination between individuals with and without ADHD, correctly classifying over 85% of individuals. While the Creyos ADHD protocol does not automate diagnosis, it may contribute to a diagnostic process with high sensitivity and specificity.

D. How Each Marker is Linked With ADHD

This section outlines the tasks included in the protocol, their associated markers, and how those markers will differ in individuals diagnosed with ADHD. It also includes references to scientific papers that contain more detail.

SPATIAL PLANNING

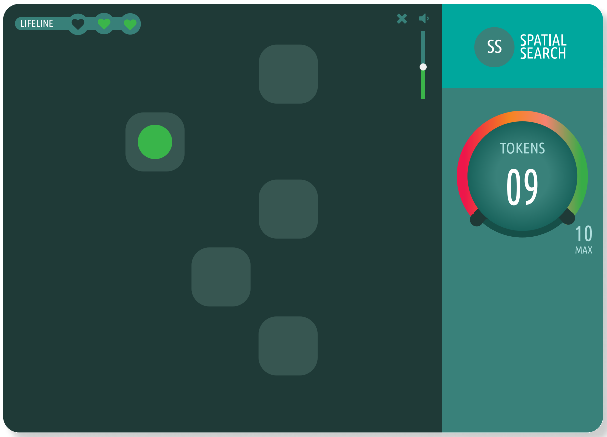


Overall Score

Marker calculation: In Spatial Planning, patients test their planning ability by moving spheres on branches, solving puzzles similar to the classic Tower of London task. The overall score is the total number of points scored during the task. Points are awarded to each correctly-solved puzzle, with more points awarded for more difficult puzzles.

Relationship with ADHD: Planning is the ability to act with forethought and sequence behavior in an orderly fashion to reach specific goals. It is a key component of executive functioning. While planning deficits are not defining features of ADHD, people with attentional difficulties may also struggle with planning tasks. In a review by Patros et al. (2019), children diagnosed with ADHD performed worse than typically developing children on tower tasks similar to Spatial Planning. However, the magnitude of the difference depended on several factors—not all individuals with ADHD will demonstrate planning deficits. The overall score on Spatial Planning can be used as a proxy for executive functioning, and may help determine whether suspected deficits are exclusive to attention tasks or if performance in non-attention tasks is below average as well.

TOKEN SEARCH

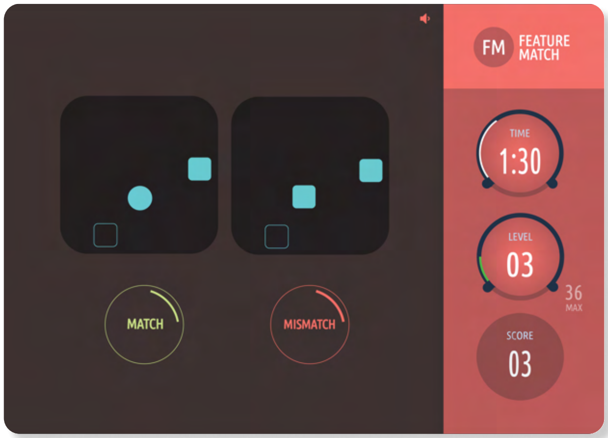


Average Score

Marker calculation: In Token Search, patients test their working memory by searching for tokens hidden among an array of boxes. Average score is the average number of boxes in which all tokens were located without error.

Relationship with ADHD: Token Search measures spatial working memory ability. Working memory is the ability to temporarily hold and manipulate information in memory, and it is a key component of executive functioning. Token Search involves self-directed searching, so there is a strategy component as well. While working memory issues are not defining features of ADHD, there has been increased interest in cognitive deficits outside of attention in these patients. Alderson et al. (2013) reviewed 38 studies of working memory, and found an overall moderate difference between adults diagnosed with ADHD and healthy controls. Several moderating variables were found, suggesting that not all individuals diagnosed with ADHD have working memory deficits in all conditions. The overall average score on Token Search can be used as a measure of the working memory component of executive functioning, and may help determine if an individual is struggling only with attention tasks, or if working memory is below average as well.

FEATURE MATCH



Number of Errors

Marker calculation: Feature Match asks patients to identify whether two sets of shapes are the same or different. The number of errors is simply the count of incorrect responses.

Relationship with ADHD: Feature Match measures short-term attention, and the number of errors represents accuracy on the task. Responding inaccurately in a brief attention task is associated with an ADHD diagnosis in both children (Langley et al., 2004) and adults (Young, Channon, & Toone, 2000).

Reaction Time

Marker calculation: Reaction time on Feature Match is calculated as the average time taken to respond correctly.

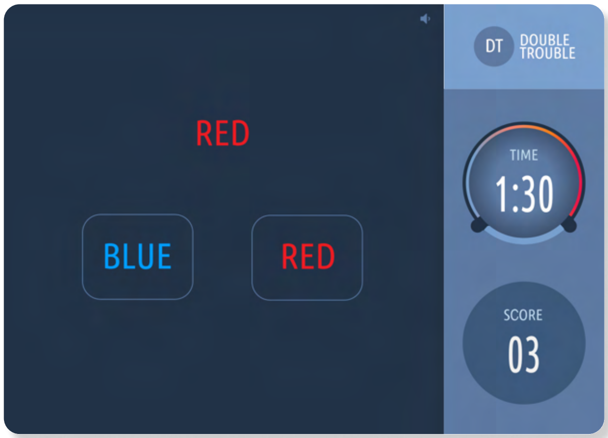
Relationship with ADHD: Feature Match's reaction time represents the speed of responding to a simple task. Children with ADHD tend to take less time to respond on simple attention tasks, but the increased speed often comes at the expense of accuracy (Langley et al., 2004).

Impulsivity

Marker calculation: If a patient is outside of the typical range on both number of errors and reaction time in Feature Match, then the impulsivity marker is flagged.

Relationship with ADHD: The impulsivity marker provides an additional layer of insight by combining accuracy and speed into one marker. A fast and inaccurate style of responding is related to impulsive behavior, and may be a symptom of ADHD (Langley et al., 2004, Mansour et al., 2021)

DOUBLE TROUBLE



Number of Errors

Marker calculation: In Double Trouble, patients test their response inhibition by identifying the ink color of the word at the top by choosing the word describing that color at the bottom (e.g., if the top word is written in the color red, then choose the word "RED" at the bottom). More difficult items require the patient to ignore incongruent information (e.g., the word "RED" written in the color blue). The number of errors represents mistakes made in response to any type of stimulus whether the color and word are congruent or incongruent.

Relationship with ADHD: Double Trouble measures response inhibition, but the number of errors represents overall accuracy in a challenging task. Making mistakes in a complex task has been associated with ADHD in children (Shallice et al., 2002) and adults (Agha et al., 2023).

Interference Ratio for Errors

Marker calculation: In Double Trouble, the patient is presented with four types of stimuli in random order. Congruent trials are those in which all words are consistent with the color they are written in: RED written in red or BLUE written in blue. Incongruent trials are those in which a word is inconsistent with the color it is written in: RED written in blue or BLUE written in red. Either the word at the top or the two words at the bottom can be inconsistent. Double incongruent trials are those in which all words are inconsistent, and is the condition that requires the most response inhibition. The interference ratio for errors is the ratio of errors in double incongruent trials to congruent trials (incongruent trials are currently ignored). A higher ratio represents responding less accurately on double incongruent trials—that is, making more mistakes when response inhibition is required.

Relationship with ADHD: Compared to the general population, individuals diagnosed with ADHD tend to make more mistakes when response inhibition is required. This effect has been detected in children (Homack & Riccio, 2003), and may be stronger in children than in adults (Lansbergen et al., 2007). This marker is an accuracy-based measure of response inhibition.

Overall Reaction Time

Marker calculation: Reaction time on Double Trouble is calculated as the average time taken to respond correctly, regardless of trial difficulty.

Relationship with ADHD: Speed of responding in complex attention tasks has been associated with an ADHD diagnosis in children and young adults (Pocklington & Maybery, 2007, Shallice et al., 2002). Unlike in simpler attention tasks like Feature Match, individuals diagnosed with ADHD tend to respond slower in tasks similar to Double Trouble. Some research has also found that children already diagnosed with ADHD who have faster reaction times may respond better to medication (Elliot et al., 2017).

Interference Ratio for Reaction Time

Marker calculation: The ratio of reaction time in double incongruent trials to congruent trials (as defined in the Interference Ratio for Errors section above). A higher ratio represents slower responses on double incongruent trials—that is, slowing down when response inhibition is required.

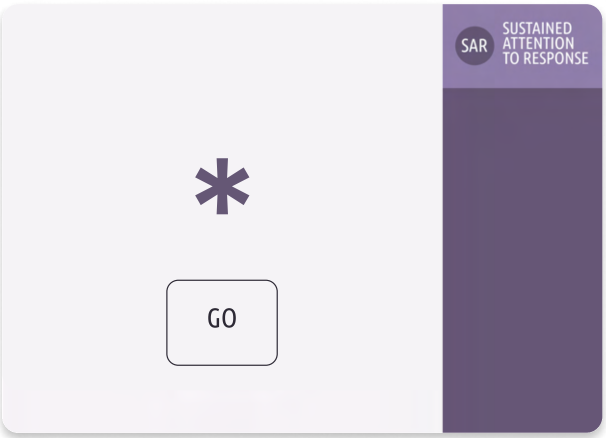
Relationship with ADHD: Compared to the general population, individuals diagnosed with ADHD tend to respond slower to stimuli requiring response inhibition. This effect appears to be consistent in both children and adults (Lansbergen et al., 2007). This marker is a speed-based measure of response inhibition.

Reaction Time Variability

Marker calculation: Reaction time variability in Double Trouble is calculated as the standard deviation of the individual's reaction times for correct responses. Higher values represent more variability in reaction times.

Relationship with ADHD: The variability of reaction times in complex attention tasks has been associated with ADHD in children (Borella et al., 2012). Although this may be partially due to taking longer on more challenging stimuli, as reflected in the interference ratio for reaction time, this marker incorporates all correct responses. Higher values may be due to more frequent abnormally long reaction times due to distraction or loss of attention, and not response inhibition specifically.

SART



Commission Errors

Marker calculation: A commission error is defined as an inappropriate response to a non-target stimulus. In the SART, this occurs when the patient hits the "go" button in response to the number 3, which they are instructed to withhold a response to.

Relationship with ADHD: Individuals diagnosed with ADHD tend to make a higher number of commission errors than the general population. Commission errors are associated with ADHD in children and adolescents (Wilcutt et al., 2005; Racicka-Pawlukiewicz et al., 2021) as well as adults (Boonstra et al., 2005; Agha et al., 2023), even after controlling for other variables, such as reaction time variability (Klein et al., 2006).

Omission Errors

Marker calculation: An omission errors is defined as failing to respond to a target stimulus. In the SART, this occurs when the patient does not hit the "go" button in response to any number other than 3. They are instructed to respond to every number except 3.

Relationship with ADHD: Compared to the general population, individuals diagnosed with ADHD tend to make more omission errors. This marker is associated with ADHD in children, adolescents, and adults (Wilcutt et al., 2005; Johnson et al., 2007; Agha et al., 2023), but this relationship may be less strong than it is with commission errors, and may be partially explained by intelligence or reaction time difficulties (Klein et al., 2006).

Reaction Time Variability

Marker calculation: Reaction time variability in the SART is calculated as the standard deviation of the individual's reaction times for correct responses. Higher values represent more variability in reaction times.

Relationship with ADHD: Individuals with ADHD tend to be more variable in their reaction times compared to the general population and to individuals with related diagnoses (Racicka-Pawlukiewicz et al., 2021; Johnson et al., 2017). Among variables from continuous performance tasks, reaction time variability is one of the best predictors of an ADHD diagnosis (Klein et al., 2006; Machida et al., 2022).

Slowing After Errors

Marker calculation: Slowing after errors on the SART is calculated as the difference between average reaction time after any correct response and average reaction time after a commission error. Higher values represent responding slower after an error, and negative values indicate speeding up after an error.

Relationship with ADHD: After making an error, most individuals slow down in an attempt to be more careful about the next response, but those diagnosed with ADHD may often fail to adjust their behavior after making a mistake. Children with ADHD tend to slow down less—or even speed up—after making a commission error on the SART (Shallice et al., 2002).

Already using Creyos and want to better understand how the ADHD protocol and report works? Email us at **help@creyos.com.**

Email **contact@creyos.com** to request a demo.